Déficit de Vitamina B12 en consumo de Metformina e Inhibidores de Bomba de Protones

Vitamin B12 Deficiency in consumption of Metformin and Proton Pump Inhibitors

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Abstract

The spectrum of diseases associated with vitamin B 12 deficiency is broad and ranges from no symptoms to malabsorption syndrome, spinal cord failure, or neurological symptoms accompanied by paresthesias, myelopathy, or neuropathy. There is suggestive evidence that long-term use of proton pump inhibitors (PPIs) may decrease serum vitamin B12 levels. Likewise, previous studies have associated vitamin B12 deficiency to high doses of metformin; however, the mechanism by which the decompensation is generated is not clear. An additive association of administration of proton pump inhibitors/histamine-2 receptor antagonists and metformin has been described, suggesting that they promote vitamin B 12 malabsorption. Both categories of drugs are widely used, in many cases without prescription, and their use should not be overlooked. When clinically indicated, their use should be monitored because of the possibility of vitamin B 12 malabsorption and its consequences. Therefore, this article reviews general aspects of vitamin B12 and the state of the art on vitamin B12 deficiency in patients taking metformin or using proton pump inhibitors.

Key words: Vitamin B12; Metformin; Proton Pump Inhibitors; Deficiency; Adverse effects; Drug Interactions.

Resumen

El espectro de enfermedades asociadas con la deficiencia de la vitamina

B 12 es amplio y abarca desde la ausencia de síntomas hasta el síndrome de malabsorción, insuficiencia medular, o síntomas neurológicos acompañados de parestesias, mielopatía o neuropatía. Existe evidencia sugestiva que indica que el empleo de inhibidores de bomba de protones (IBP) a largo plazo puede disminuir los niveles séricos de vitamina B12. Igualmente, estudios previos han asociado el déficit de vitamina B 12 a consumo en dosis altas de metformina, sin embargo, el mecanismo por el cual se genera la descompensación no está claro. Se ha llegado a describir una asociación aditiva de la administración de inhibidores bomba de protones/ Antagonistas receptor Histamina - 2 y metformina, sugiriendo que promueven la malabsorción de Vitamina B 12. Ambas categorías de medicamentos son ampliamente utilizadas, y en muchos casos sin prescripción médica, y su uso no debería ser pasado por alto. Cuando están clínicamente indicados, su uso debería ser monitorizado debido a la posibilidad de malabsorción de vitamina B 12 y sus consecuencias. Por tanto, en este artículo se revisan aspectos generales sobre la vitamina B12 y el estado del arte sobre la deficiencia de vitamina B12 en pacientes con consumo de metformina o uso de inhibidor de bomba de protones.

Palabras claves (DeCS): Vitamina B12; metformina; inhibidores bomba de protones; deficiencia; efectos adversos; interacciones farmacológicas

Introduction

Vitamin B 12 or cobalamin (B12) is a cofactor for two enzymes: methionine synthetase and L-methylmalonyl-coenzyme A mutase (1). The spectrum of diseases associated with vitamin B 12 deficiency is broad and ranges from no symptoms to malabsorption syndrome, spinal cord failure, or neurological symptoms accompanied by paresthesias and signs of myelopathy or neuropathy (2,3).

Proton pump inhibitors (PPIs) are the most potent suppressors of gastric acid secretion; at usual doses, they decrease acid production by 80 to 95%. These medicines are among the most frequently prescribed medications in the world. They are usually used in the long-term treatment of several acid peptic disorders including gastroesophageal reflux disease, peptic ulcers and hypersecretory states such as Zollinger Ellison syndrome (4). Long-term use of PPIs is effective and safe. However, there is suggestive evidence that their long-term use may result in decreased serum B 12 levels (2,3,5,6).

The prevalence of vitamin B12 deficiency varies globally from 5.8% to 30% in patients on long-term metformin therapy (7,14). Identifying vitamin B12 deficiency is clinically relevant because of the various conditions that

may be associated with its presentation, such as megaloblastic anemia, neuropathy, cognitive impairment, memory loss, irritability, dementia, extrapyramidal signs, and increased risk of osteoporosis (12, 14). It should be noted that the mechanism by which metformin consumption is associated with vitamin B12 deficiency is not clear.

An additive association of administration of proton pump inhibitors/histamine-2 receptor antagonists and metformin has even been described, suggesting that they promote vitamin B12 malabsorption. Both categories of medications are widely used, and in many cases without prescription, and their use should not be overlooked. When clinically indicated, their use should be monitored because of the possibility of vitamin B12 malabsorption and its consequences (15). Recognition and treatment of vitamin B12 deficiency is critical because it is a reversible disorder (2). Therefore, this article reviews general aspects of vitamin B12 and the state of the art on vitamin B12 deficiency in patients taking metformin or proton pump inhibitors.

Vitamin B12 metabolism

The vitamin B12 absorption cycle begins with the release of protein bound vitamin B12 from foods that require gastric acid and pepsin in the stomach. Free vitamin B12 then binds to salivary haptocorrin, which protects vitamin B12 from stomach acid as it is transported to the small intestine. In the small intestine, vitamin B12 binds to intrinsic factor produced by gastric parietal cells. In the ileum, the intrinsic factor-vitamin B12 complex binds to the specific receptor known as cubilin on the ileal mucosa and is internalized and subsequently released into the circulation (2,15,16).

There is a second absorption pathway by passive diffusion that occurs throughout the intestine and accounts for approximately 1% of total absorption; this pathway is not affected in pernicious anemia and justifies oral vitamin B12 therapy (2,15,16).

A 3-9 mcg of vitamin B12 is lost in the bile each day, which is reabsorbed in the ileum (enterohepatic circulation) after absorption, vitamin B12 binds to either of 2 transport proteins (transcobalamin or haptocorrin) to be transported throughout the body (16).

Vitamin B12 bound to Transcobalamin forms holotranscobalamin, the me-

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tabolically active form of vitamin B12, which normally accounts for about 20% of total plasma levels of vitamin B12; only Transcobalamin can facilitate absorption into cells through endocytosis mediated by the Transcobalamin receptor.

Vitamin B12 bound to haptocorrin is metabolically inactive (not available for cellular uptake) and typically accounts for 80%-94% of endogenous plasma vitamin B12 (17).

Humans generally have large stores of vitamin B12 (approximately 1-5 mg), so deficiency due to malabsorption or decreased intake may not manifest for several years after the depletion of stores. The wide spectrum of clinical manifestations may be explained by genetic variation and acquired comorbidities (15,16,18).

Metabolically active vitamin B12 acts as a cofactor for two enzymatic reactions that enable erythropoiesis and myelination. The methionine synthase reaction in the cytoplasm, which allows the conversion of homocysteine to methionine and the recycling of 5-methyl-tetrahydrofolate (THF) to N5,10-methylene-THF necessary for the generation of thymidylic acid, which is then used for DNA synthesis (16).

The second enzymatic reaction corresponds to the methylmalonyl CoA mutase reaction in mitochondria - conversion of methylmalonyl CoA to succinyl CoA, a precursor for the synthesis of the heme group and fatty acids (15,16).

The homocysteine pathway blockade leads to elevated homocysteine levels. The blockade of the L-methylmalonyl-coenzyme A pathway leads to hydrolysis of excess L-methylmalonyl-coenzyme A, resulting in elevated levels of methylmalonic acid (15,16).

There are multiple processes involved in achieving and maintaining normal vitamin B12 levels, the first of which includes adequate dietary intake of vitamin B12, being microorganisms (bacteria and archaea) the main source of vitamin B12 in nature (3), it is also found in animal products (meat, fish, and dairy products) or supplements. It should be mentioned that the Western diet contains about 5-30 mcg of vitamin B12 per day, of which 1-5 mcg is absorbed, the recommended daily amount varies from 0.4 mcg/day in infants to 2.4 mcg/day in adults, 2.6 mcg/day for pregnant women, and 2.8 mcg/day for lactating women. About 1-5 mg are stored in the body, with about half stored in the liver (18).

Clinical approach to Vitamin B12 deficiency

Disruption of one or more steps in the absorption or transport cycle can result in clinical and biochemical effects of vitamin B12 deficiency. The hematological effect of vitamin B12 deficiency is megaloblastic anemia due to defective DNA synthesis. Dyssynchronous maturation of the nucleus and cytoplasm results in intramedullary apoptosis of megaloblastic erythroid precursors (ineffective erythropoiesis), leading to intramedullary hemolysis and release of lactate dehydrogenase, macrocytosis, anemia, and hypersegmentation of neutrophils in the peripheral blood. Additionally, there is an increase in red cell membrane stiffness leading to a 30% -50% reduction in red cell lifespan (16,18).

Neurological effects may occur before hematological effects arise and may occur in the absence of hematological complications, these effects are due to defective initiation and maintenance of myelination of central and peripheral neurons. White matter (long tracts found in the posterior and lateral columns of the spinal cord), which contain sensory neurons involved in the conduction of vibration and position, are especially susceptible to demyelination (18,19).

When vitamin B12 deficiency is suspected, a complete blood count and peripheral blood smear should be performed, as well as a serum vitamin B12 level; a low level can confirm the diagnosis, but the assay has limited diagnostic accuracy and suggested cut-off levels vary (16). Therefore, consideration should be given to evaluating increased methylmalonic acid or total plasma homocysteine levels (weak recommendation) or decreased holotranscobalamin level (18). If vitamin B12 deficiency is confirmed but the etiology is unclear, additional blood tests may be necessary to help identify the underlying cause (18) .

Problem magnitude

Vitamin B12, also called cobalamin, is an important cofactor for DNA synthesis and cell metabolism. The most common clinical effects of vitamin B12 insufficiency are anemia and demyelinating nervous system disease. The most common cause of severe vitamin B12 deficiency is pernicious anemia due to a loss of intrinsic factor in autoimmune atrophic gastritis (18,19).

Other causes of vitamin B12 deficiency include altered gastrointestinal absorption due to gastric or ileal resection, medications that interfere with vitamin B12 absorption or affect serum levels, including long-term use of antacids, H2-receptor antagonists, or proton pump inhibitors (PPIs), and metformin. Other associated factors are vegan or vegetarian diets, states that in-

clude increased vitamin B12 requirements such as pregnancy, and hereditary causes of impaired vitamin B12 absorption or metabolism (15,18).

Presentations vary widely in type and severity, but vitamin B12 deficiency often presents as: macrocytic anemia, with or without symptoms (such as fatigue or dyspnea), neuropsychiatric findings such as paresthesias, gait disturbances, sensory deficits, mild cognitive impairment, depression, or dementia (18,19). It has been recognized hematological, metabolic, and neurological alterations in patients with vitamin B12 deficiency. Among the hematological manifestations, it has been associated with megaloblastic anemia, associated with elevated bilirubin of indirect predominance, elevated LDH secondary to intramedullary hemolysis, leukopenia and thrombocytopenia (16).

The prevalence of vitamin B12 deficiency increases with age and is particularly higher in older adults, for example, in a descriptive study in Brazil it was 17.4% (20). Studies conducted so far have found no differences in the prevalence of vitamin B12 deficiency in terms of sex (21,22).

Proton Pump Inhibitors (PPIs) in relation to Vitamin B12 deficiency

The inhibition of gastric acid secretion by PPIs can promote cobalamin malabsorption by different mechanisms (2,3). One of them is elevation of intragastric pH, which alters the extraction of B12 from dietary proteins and in turn the reduction of gastric acid alters the intestinal microbiota. It may also predispose to small intestinal bacterial overgrowth, which in turn increases bacterial consumption of B12 (2,3). Another mechanism implicated in the reduction of B12 levels in patients with PPI use is the reduction of parietal cell activity, which may reduce intrinsic factor secretion (14).

The potential for PPIs to interact with other drugs has highlighted multiple mechanisms involved. Possibilities include altered absorption through changes in gastric pH and altered hepatic metabolism of the drug through CYP2C19 and other enzymes (23). Interactions with other CYP isoforms have been documented, and vary among different PPIs, making it possible that drug-drug interactions are specific to different PPIs (24).

Nies et al, (2011) demonstrated that PPIs can inhibit OCT1 , OCT2 , and OCT3 in-vitro at half the minimum inhibitory concentration (IC50). Beyond this, PPIs affect the gastrointestinal absorption of many classes of medications by altering gastric pH (25). These findings suggest that coadministration of metformin with PPIs may cause drug-drug interactions.

In 2010 Martinez et al. conducted a study that calculated the prevalence of vitamin B12 deficiency in patients with chronic atrophic gastritis according

to the Sydney criteria finding a prevalence of 28% (22).

At the National University of Colombia, in the external consultation service of the Los Fundadores clinic, a descriptive study was carried out that included patients with a diagnosis of gastrointestinal disease and PPI consumption, which reported a decrease in B12 levels in patients with PPI consumption for more than 3 years, corresponding to 27.8%. No significant differences were found between the type of PPI or the doses used in terms of vitamin B12 levels (21).

Association of Metformin consumption with vitamin B12 deficiency

Metformin is an oral insulin-sensitizing agent and is used for the treatment of type 2 diabetes mellitus as monotherapy or in combination therapy. Its main mechanism of action is to decrease hepatic glucose production and glucose absorption from the gastrointestinal tract, and to increase insulin sensitivity and peripheral glucose consumption (26).

Metformin does not undergo hepatic metabolism and it is excreted unchanged in the urine. Its uptake in the liver is mediated by organic cation transporter 1 (OCT1). Genetic variations in OCT1 are associated with differences in metformin pharmacokinetics (27); whereas OCT2 is expressed in the kidney and contributes to the renal elimination of metformin (28,29).

The prevalence of vitamin B12 deficiency in patients with type 2 diabetes mellitus has been considered higher than in non-diabetic patients (8,30,32). However, the related mechanisms are not well established. Some evidence suggests the hypothesis that metformin induces vitamin B12 malabsorption due to increased bacterial overgrowth or modification of the intestinal microbiota (31,33,34). It should be noted that metformin interferes with calcium-dependent membrane action potential and intrinsic factor-vitamin B12 secretion per se. Since the intrinsic factor-vitamin B12 complex reuptake of the ileal cell surface receptor is a calcium-dependent process, both mechanisms possibly cause a decrease in the absorption of vitamin B12 (35,36) .

Previous studies have associated vitamin B12 deficiency with high-dose metformin intake. DeFronzo and Goodman found that while metformin provides good glycemic control, vitamin B12 concentrations can be lowered by up to 22% compared to placebo (37). On the other hand, a clinical trial designed to examine the temporal relationship between Metformin and vitamin B12 found a 19% reduction in vitamin B12 levels when compared to placebo after 4 years of treatment (38).

In a cross-sectional cohort study comparing the prevalence of vitamin B12

deficiency in 231 patients on metformin with 231 controls attending outpatient endocrinology consultation at a public university hospital in southeastern Brazil, a prevalence of 22.5% versus 7.4% in controls was reported (30).

Sanchez et al. in a case-control study conducted in two primary care centers in Santiago de Chile in older adults found 1.9 times higher risk of vitamin B12 deficiency in patients taking Metformin. The average consumption of Metformin was 1954 mg per day (39).

Regarding the duration of Metformin use, variable results have been described, even describing vitamin B12 deficiency from three to four months after the beginning of treatment (11,35). However, according to more recent reports, vitamin B12 deficiency occurs only after 5 to 10 years of metformin use (31), this delay in the time of onset of vitamin B12 deficiency may be due to significant storage of this vitamin at the hepatic level (40,41).

The simultaneous use of metformin with proton pump inhibitors or histamine-2 receptor antagonists is associated with reduced gastric acidity, with a predisposing role for vitamin B12 malabsorption. Both drugs decrease acid secretion in the parietal cell, which is required for the cleavage of vitamin B12 from the diet (1,42,43). Some other studies, such as the one performed by Nervo et al (12) showed that there is no association between serum levels of vitamin B12 and the use of omeprazole. However, considering the additive effect between the administration of proton pump inhibitors/H2 - antagonists and metformin, caution should be taken when administering these two drugs.

Conclusions

The biological plausibility of the effects of proton pump inhibitors concomitantly with metformin in reducing serum vitamin B12 levels is increasingly well described.

Prolonged consumption of proton pump inhibitors is associated with a decrease in serum vitamin B12 levels and a higher prevalence of vitamin B12 deficiency. Also, it is necessary to consider the possibility of vitamin B12 absorption deficiency in patients on metformin treatment.

The importance of reviewing the drugs taken by our patients and their side effects when symptoms appear before adding a new drug or resorting to complementary tests should be emphasized.

Further studies are needed to establish how much the serum Vitamin B12 concentration is altered in patients treated with proton pump inhibitor or Metformin for a certain period of time.

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